IN THE SPECIFICATION:

Please amend the specification as indicated hereinbelow.

Please AMEND the paragraph at page 4, lines 14-22 to read as follows:

Thus, compositions ~~as defined in the appending claims meet the objective of the invention, such a composition comprising~~ according to the invention comprise a solution of saline in a physiologically acceptable concentration and a protein having a colloid osmotic function characterized in that the compound having a protein colloid osmotic function is a recombinant gelatin-like protein with an isoelectric point of less than 8 and a molecular weight from at least 10,000 Daltons to 25,000 Daltons or at most 50,000 Daltons. In a further aspect the invention concerns a dimer or a trimer or a tetramer of a recombinant gelatin-like protein with an isoelectric point of less than 8 and a molecular weight from at least 10,000 Daltons to 25,000 Daltons, or at most 50,000 Daltons.

Please AMEND the paragraph at page 8, lines 7-20 to read as follows:

In order to maintain a suitable colloid osmotic pressure in combination with a targeted clearance rate from the blood circulation system when administered to a subject, the molecular weight of a gelatin-like molecule for use according to the invention should be at least 10,000 Daltons, preferably more than 20,000 Daltons, more preferably more than 30,000 Daltons. Even more preferably the molecular weight is between about 30,000 Daltons and 120,000 Daltons. ~~Obviously to~~ To reach molecular weights of more than 50,000 Daltons a multimer, at least a dimer, of the gelatin-like protein ~~defined in claim 1 has to be~~ employed in the invention is prepared. Preferably, the gelatin-like molecule for use according to the invention has a low amount of hydroxyproline residues, meaning that less than 10% of the aminoacid residues in the polypeptide are hydroxyproline residues. The amount of hydroxyprolines is restricted to prevent gelation of the recombinant gelatin. It is preferred to avoid gelation, since this limits the concentration in which the plasma expander can be applied or requires warming of the plasma expander solution before administering.

Please AMEND the paragraph at page 9, lines 4-9 to read as follows:

In order to maintain a suitable colloid osmotic pressure in combination with a targeted clearance rate from the blood circulation system when administered to a subject, the molecular weight of a gelatin-like molecule for use according to the invention should be at least 10,000 Daltons, preferably more than 20,000 Daltons, more preferably more than 30,000 Daltons. Even more preferably the molecular weight is between about 30,000 Daltons and 120,000 Daltons. ~~Obviously to~~ To reach molecular weights of more than 50,000 Daltons a multimer, at least a dimer, of the gelatin-like protein ~~defined in claim 1 has to~~ having a colloid osmotic function, being a recombinant gelatin-like protein with a molecular weight of from at least 10,000 Daltons to at most 50,000 Daltons and having an isoelectric point of less than 8, can be prepared. Preferably, the gelatin-like molecule for use according to the invention has a low amount of hydroxyproline residues, meaning that less than 10% of the aminoacid residues in the polypeptide are hydroxyproline residues. The amount of hydroxyprolines is restricted to prevent gelation of the recombinant gelatin. It is preferred to avoid gelation, since this limits the concentration in which the plasma expander can be applied or requires warming of the plasma expander solution before administering.

Please AMEND the paragraph at page 9, lines 4-9 to read as follows:

As mentioned earlier, plasma substitution compositions comprising gelatins can be lethal to subjects having an allergy or an auto-immune disease. When pursuing the approach of recombinant production of gelatins and bearing in mind that such gelatins should be even less immunogenic in human subjects than the presently used bovine derived gelatins, it is obvious to take up production of recombinant human gelatin. In addition it is obvious not to induce marked changes in the basic gelatin structure.

Please AMEND the paragraph at page 9, line 30 to page 10, line 16 to read as follows:

With respect to the design of gelatin-like proteins for use in the invention, several properties of the proteins are addressed. For instance the clearance speed of the gelatin-like proteins can be

"designed-in" by the choice for a specific size or a specific range of sizes of the gelatin-like proteins. In particular this could be advantageous in combination with known nephrotic system characteristics (measured by for instance the creatinine clearance pattern) of subjects to whom the gelatin-like proteins are administered. The size of the gelatin-like protein can be designed by multimerisation of a specific monomer (which can also be regarded as a block polymer), representing for instance a specific part of a native human collagen. A ~~serie~~ series of plasma expanders, each of them with a well defined clearance characteristic can be designed by step by step increase of the number of monomers in the multimeric, complete plasma expanders, consisting of one, two, three, four and more monomers of a gelatin-like protein. The monomer amino acid (AA) sequence can be chosen from the human collagen sequence, by selecting an AA domain with a low ~~IEP~~ iso-electric point (IEP) of the polypeptide and a low sensitivity to any proteolytic activity, which could be present in the unicellular production system of interest for example, yeast, fungi and others. The size of the gelatin-like proteins is further of importance for the colloid osmotic pressure, as discussed herein, it exercises. Yet further the iso-electric point (IEP) and number of aminoacids with an ionizable residual group can be tuned by the composition of acidic and basic amino acid residues in the gelatin-like proteins.

Please AMEND the paragraph at page 12, lines 1-23, to read as follows:

The gelatin-like proteins for use according to the invention can be produced by recombinant methods as disclosed in ~~EP-A-0926543, EP-A-1014176~~ van Heerde et al. US Patent No. 6,051,081 ("US 6,051,081") or WO01/34646. Also for enablement of the production and purification of gelatin-like proteins that can be suitably used in composition according to the invention reference is made to the examples in ~~EP-A-0926543 and EP-A-1014176~~ US 6,051,081. Thus the gelatin-like proteins can be produced by expression of nucleic acid sequence encoding such polypeptide by a suitable micro-organism. The process can suitably be carried out with a fungal cell or a yeast cell. Suitably the host cell is a high expression host cells like *Hansenula, Trichoderma, Aspergillus, Penicillium, Neurospora* or *Pichia*. Fungal and yeast cells are preferred to bacteria as they are less susceptible to improper expression of repetitive sequences. Most preferably the host will not have a high level of proteases that attack the collagen structure expressed. In this respect *Pichia* or *Hansenula* offers an example of a very suitable expression

system. Use of *Pichia pastoris* as an expression system is disclosed in ~~EP-A-0926543 and EP-A-1014176~~ US 6,051,081. Preferably the micro-organism is free of active post-translational processing mechanism such as in particular hydroxylation of proline and also hydroxylation of lysine. The host to be used does not require the presence of a gene for expression of prolyl-4-hydroxylase Preferably the host also does not require the presence of lysyl-hydroxylase. The selection of a suitable host cell from known industrial enzyme producing fungal host cells specifically yeast cells on the basis of the required parameters described herein rendering the host cell suitable for expression of recombinant gelatin-like proteins suitable in compositions according to the invention in combination with knowledge regarding the host cells and the sequence to be expressed will be possible by a person skilled in the art.

Please AMEND the paragraph at page 17, lines 23-25 to read as follows:

Human recombinant gelatin-like polypeptides Hu-1 (SEQ ID NO: 1), Hu-3 (SEQ ID NO: 2), Hu-4 (SEQ ID NO: 3) and Hu-deam (SEQ ID NO: 4) was produced by recombinant methods as disclosed in ~~EP-A-0926543 or EP-A-1014176~~ US 6,150,081.

Please AMEND the paragraph at page 14, lines 31-33 to read as follows:

Many ~~bloodplasma~~ blood plasma proteins have a transport function. Low isoelectric point reduces the chance that the gelatin-like protein interacts with these blood plasma proteins and thereby the chance that the blood plasma proteins function is hindered.

Please AMEND the paragraph at page 15, lines 1-17 to read as follows:

A possible explanation for the lower clearance rate of the gelatin-like proteins according to the invention is the nature of the glycocalyx barrier that lines the walls of ~~bloodvessels~~ blood vessels. This glycocalyx regulates the transport of substances like solutes and proteins between ~~bloodvessels~~ blood vessels and the surrounding tissue. The exact functions of the glycocalyx and the mechanisms by which such functions are performed have not been elucidated. Interaction between glycocalyx and foreign proteins like gelatins from plasma expander are therefore better avoided. Gelatin-like proteins according to the invention have less interaction with the

glycocalyx which serves to reduce the transport of gelatin-like proteins from the blood to the surrounding tissue. An increase of the total surplus of negative charge of the gelatin-like plasma expander at pH 8, by for instance replacing Gln by Glu or Asn by Asp is a method to decrease the interaction between the plasma expander and the glycocalyx further and to increase the intravascular half life time of the plasma expander. Also (temporary) damage of the glycocalyx by gelatin-like proteins according to the invention is prevented by repulsion of said gelatin-like proteins by the glycocalyx. Such (temporary) damage would increase the circulating blood volume containing plasma expander, resulting in an undesired decrease in blood pressure.

Please AMEND the table comprising the whole of page 22 and page 23 down to but not including "LABORATORY INVESTIGATION" to read as follows:

TEST / CONTROL / COMPARISON SOLUTIONS

Test solution 1	recombinant human gelatin, 55.2 kD Hu-3
identity	Hu-3, 55.2 kD
supplier	Fuji
formulation	freeze dried
remarks	reconstituted with 0.9% NaCl at 4 g/100ml and stored at ~~4oC~~ 4 °C until adminstration (for less than 1 week)
Test solution 2	recombinant human gelatin, 73.6kD Hu-4
identity	Hu-4 73.6kD
supplier	Fuji
formulation	freeze dried
remarks	reconstituted with 0.9% NaCl at 4 g/100ml and stored at ~~4oC~~ 4 °C until adminstration (for less than 1 week)
Test solution 3	recombinant human gelatin. deamidated, 48 kD Hu-deam
identity	Hu-deam

supplier	Fuji
formulation	freeze dried
remarks	reconstituted with 0.9% NaCl at 4 g/100ml and stored at ~~4oC~~ 4 °C until adminstration (for less than 1 week)
Control solution	saline
identity	0.9% (w/v) NaCl
supplier	NPBI, Emmer-Compascuum, The Netherlands
formulation	sterile fluid for iv administration
remarks	
Comp solution 1	human albumin
identity	Cealb
supplier	CLB
formulation	solution for iv infusion, 20 g/100ml
remarks	stored at ~~4oC~~ 4 °C, diluted with saline to 5 g/100mL
Comp solution 2	modified bovine gelatin
identity	Gelifundol
supplier	Biotest Pharma GmbH
formulation	solution, 5.5 g/100 ml
remarks	stored at ~~4oC~~ 4 °C, diluted with saline to 4 g/100mL

Please AMEND the paragraph at page 14, lines 31-33 to read as follows:

The hematocrit at each time point is calculated from the ~~rbc~~ red blood cell count at that time point, the red blood cell (rbc) count at t=0 and the hematocrit at ~~t=0~~ t=0.